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09/843,462	04/25/2001	Barbara A. Foster	PC10583ADAM	8327

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EXAMINER
COOK, LISA V

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1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/843,462	Applicant(s) FOSTER ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office action mailed 4 November 2002 is acknowledged. (See paper#10, filed 5/9/03). In amendment-A filed therein non-elected claims 9-19 and 21-23 were canceled. A Declaration under 37 CFR 1.131 and substitute Oath and Declaration were also filed. Currently claims 1-8 and 20 are pending and under consideration.

OBJECTIONS MAINTAINED

Applicants have not responded to the objections below. Accordingly the following objections are maintained.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

3. The information disclosure statements filed in paper #3 on 5/7/01 and in paper #4 on 6/25/02 have been considered as to the first action on the merits.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademarks has been noted in this application. (see - NUNC on page 7, Tween on page 8, and Pharminogen on page 12 - for examples). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

OBJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 recites the limitation "a method for measuring cyclin-dependent kinase (CDK) activity". However the claim merely reads on the measurement of a complex formed between the sample, an anti-retinoblastoma protein (Rb) capture antibody, and an anti-Rb primary antibody. A correlation step with respect to how CDK activity will be measured via the complex is not recited. Therein it is unclear if applicant intends to measure CDK activity or simply antibody detection of a retinoblastoma protein in a given sample. Please clarify.

B. Claim 1 step (iii) recites the limitation "CDK-phosphorylated Rb" in claim 1. There is insufficient antecedent basis for this limitation in the claim. The claim does not mention a CDK-phosphorylated Rb complex nor does it indicate that the retinoblastoma protein complex formed in step (ii) undergoes phosphorylation.

Response to Argument

Applicant contends that the relationship of Rb and CDK activity is clear because the capture antibody recognizes only Rb phosphorylated at specific CDK phosphorylation sites. Therefore as the amount of CDK increases, so does the amount of Rb. This argument was carefully considered but not found persuasive because the claims do not recite specific CDK phosphorylation sites specifically recognized by the capture antibody. The present claims merely require an Rb capture antibody. In response to applicant's argument, it is noted that the features upon which applicant relies (i.e., specific CDK phosphorylation sites) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The rejection is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 4-7, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998).

Wen et al. teach an ELISA (enzyme linked immuosorbent assay) to detect $p110^{RB}$ (retinoblastoma protein). ELISA methods are taught in the instant specification (see page 6, figure 1) A coating antibody (anti-retinoblastoma protein (Rb) capture antibody) in combination with a 3C8 monoclonal antibody (anti-Rb primary antibody) is used to measure the retinoblastoma protein. See page 235, Section 3.3

Wen et al. differ from the instant invention in not specifically teaching the correlation of retinoblastoma protein to cyclin-dependent CDK activity.

However, Juan et al. disclose a method to measure the in situ phosphorylation state of retinoblsatoma protein (pRb). This is accomplished by employing dual antibodies simultaneously to detect pRb. One antibody specifically detects underphosphorylated forms of the protein (pRb^{P-}) and the other reacts with total (pRb^{T}). The conjugation of these anti-pRb mAbs with fluorochromes of different color, allows for multiparametered flow cytometry analysis. See page 105, 1st paragraph, 1st column. In the method human peripheral blood lymphocytes in culture are contacted with anti-pRb^{T}conjugated to CY-Chrome and anti-pRb^{P-} conjugated with FITC. (Please see page 105, 1st column, 2nd paragraph). The fluorescence measurement can be utilized to detect agents that target CDK4 activity or other CKDs activity in pRb phosphorylation activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure CDK activity as taught by Juan et al. with the retinoblastoma protein detection method of Wen et al., because Juan et al. taught that assays to detect retinoblastoma proteins "could be applied for screening ...CDKs and monitoring retinoblastoma phosphorylation". See abstract.

Juan et al. also taught that the function of pRb is affected by its phosphorylation at serine and threonine residues by the cyclin-dependent kinases. Page 104, 2nd column 1st paragraph.

One having ordinary skill in the art would have been motivated to correlate CDK activity in retinoblastoma protein detection in order to more obtain information with respect to the function of the protein.

II. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350).

Please see Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) are set forth above.

Wen et al. in view of Juan et al. differ from the instant invention in not specifically teaching the measurement of CDK2 and CDK4 activity.

However, Watanabe et al. disclose antibodies to detect the phosphorylation of retinoblastoma protein (pRb). Applicant's Rb protein. The formed complex was further employed to measure Cdk2 and Cdk4 kinase activities. See abstract. The reference teaches that pRb contains more than 12 phosphorylation sites at serine or threonine, and is phosphorylated by cyclin-dependent kinases (Cdks) in a cell cyclin-dependent manner. Page 342, 2nd column.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure Cyclin E/Cdk2 and Cyclin D/Cdk4 activity as taught by Watanabe et al. in the retinoblastoma protein detection method of Wen et al. in view of Juan et al., because Watanabe et al. taught that "recently, consensus motifs for phosphorylation by cyclin D/Cdk4 and cyclin E/Cdk2 were determined and antibodies against pRb phosphoyalted sites were prepared".... by Kitagawa et al. (page 343, 1st column, 2nd paragraph). Juan et al. further taught that "little is known about the site specific phosphorylation of pRb in vivo during the differentiation process". (page 343, 1st column, 2nd paragraph).

Therein one having ordinary skill in the art would have been motivated to employ the known Cyclin E/Cdk2 and Cyclin D/Cdk4 antibodies directed to known sites of the retinoblastoma protein (pRb) in order to understand cyclin dependent kinase activity (cdks) in a sample. The knowledge of site specific-antibodies enhanced sensitivity with respect to where the pRb protein is being phosphorylated, therefore none relevant sites are not evaluated giving more accurate and precise detection.

III. Claims 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) and further in view of in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187).

Please see Wen et al. in view of Juan et al. as set forth above.

Wen et al. in view of Juan et al. differ from the instant invention in not specifically teaching the detection assay in test plates/micro titer plates.

However, Maggio disclose enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase/test plate. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (micro titer plates). See page 186.

Wen et al., Juan et al. and Maggio are analogous art because they are from the same field of endeavor, all three inventions teach methods immunoassay methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use micro titer plates as taught by Maggio in the assay method to detection retinoblastoma protein of Wen et al. in view of Juan et al. because Maggio taught that micro plates or micro titer plates "are very convenient to wash thereby reducing labor in assay procedures". Page 186, last line.

Response to Argument

7. The Declaration of Barbara A. Foster and Farzan Rastinejad filed on 09 May 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the Watanabe et al., Brain Research 842:342-50, 1999 reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The Declaration is not accompanied with exhibits of drawings or records, or photocopies thereof. Please see 37 CFR 1.131 Affidavit or declaration of prior invention.

b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence satisfactorily explained.

8. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that the method is drawn to phosphorylated Rb and CDK activity via Rb phosphorylation at specific residues by CDK. This argument was carefully considered but not found persuasive because the instant claims do not include "Rb phosphorylation at specific residues by CDK". In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., specific CDK phosphorylation sites) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The rejection is maintained.

In response to the argument regarding the measurement of total Rb (Wen et al.) verses specific Rb phosphorylated at specific CDK-mediated residues (Instant invention), it is noted that the claims do not distinguish between total Rb and CDK-mediated residues. In other words the specific residues are not included neither are the specific antibodies that would bind only said specific residues.

In response to the argument that Juan measures dual readouts rather than a single readout evaluation it is noted that the claims do not specify single readout extrapolation.

The rejections including Watanabe et al. (Brian Research, 842, 1999, pages 342-350) and Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187) are maintained in view of the response above. Accordingly the rejections are maintained.

9. For reasons aforementioned, no claims are allowed.

10. **THIS ACTION IS MADE NON-FINAL.**

Remarks

11. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Tanguay et al. (Journal of Immunology, 9/15/99, 163 (6) 3160-8) disclose that BCR-induced Rb phosphorylation is abrogated by co-cross-linking with Fc gamma R. The activation of Cdk4 and Cdk2 dependent Rb protein kinase is blocked.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
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7/15/03

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